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C-reactive protein and cardiovascular diseases: a synthesis of studies based on different designs

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Inflammation plays an important role in the genesis, progression, and manifestation of cardiovascular diseases (CVDs).[1] C-reactive protein (CRP), an acute phase protein produced by the liver, is one of the most extensively studied systemic markers of inflammation. CRP increases within a few hours after an inflammatory trigger, peaks in two days, and decreases rapidly with the resolution of inflammation. Over the past three decades, extensive epidemiological and clinical evidence has linked the concentration of CRP to major CVDs.[2–4] Since the 2000s, multiple cardiology organizations across the world have recommended adding CRP as an adjunct to assess or predict risks for CVDs.[5–8] However, the role of CRP in CVDs among human populations, especially whether a causal relationship between them exists, remains unclear. This leads to substantial debates on whether CRP can be used as a therapeutic target for CVDs.[9–13]

To provide some preliminary answers to the above questions, we conducted a review of studies on the relationship between CRP and CVDs. Since multiple reviews of the relationship between CRP and CVDs have been published previously,[2,3,10,14–16] our aim was neither to provide an exhaustive summary of previous studies nor to reach a consensus on the role of CRP. Instead, we want to delineate the current status of this research topic. We first summarized characteristics and findings on the relationship between CRP and CVDs from a perspective of study designs, identified their similarities and discrepancies across studies by designs, and provided our interpretations. In our opinion, the available studies do not support a causal relationship between CRP and CVDs despite a widely observed positive association between them. The comparison and synthesis of studies with different designs can facilitate appropriate interpretations of such an association.

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Studies of different designs on CRP and CVDs

Table 1 summarizes the characteristics and findings of studies on CRP and CVDs by designs, including animal experiments, traditional observational studies, Mendelian Randomization (MR) studies, and clinical trials. In the table, we presented only three representative studies of each design.

First, in animal experiments, findings are controversial regarding the relationship between CRP and CVDs.[17–22] These studies mainly applied genetic techniques to mice, rats, and rabbits and constructed animal models with a sample size ranging from several dozens to hundreds. For example, some studies showed that CRP can contribute to the pathological process of atherosclerosis,[17,18] but more studies did not observe associations between CRP and CVDs.[19–21] One study even reported that human CRP may slow the development of atherosclerosis.[22] There is no clear explanation for these contradictory findings from animal experiments. In addition, it is also challenging to generalize findings from animal experiments to humans because of substantial differences in CRPs across species with respect to ligand recognition, secondary effects of ligand binding, and others.[14] Therefore, animal experiments have not determined whether there is a causal association between CRP and CVDs.

Second, many traditional observational studies of human populations found positive associations between CRP concentrations and CVDs, including both cross-sectional and longitudinal studies.[23–25] Our search showed that to date there are at least 60 traditional observational studies that have examined the relationship between CRP and CVDs. Their number is much larger than those of studies based on other designs. Besides studies based on individual-level data, multiple meta-analyses also showed that a higher concentration of CRP is associated with an increased risk of CVDs.[26–28] These findings suggest that CRP can be a useful biomarker to assess the risk of CVDs among diverse populations. For example, the American Heart Association (AHA) previously added CRP to optimize the assessment of cardiovascular risk.[5] However, it is still challenging to infer causality based on traditional observational studies due to confounding.

Third, in the late 2000s, researchers started to use the MR method to examine the potential causal relationship between CRP and CVDs.[4] This approach assumes that if the causality between these two indeed exists, genetic variants in CRP that are associated with altered CRP levels should also be associated with altered risks for CVDs. Since genetic variants are unrelated to confounding factors, this approach is not as prone to confounding and reverse causation bias as traditional observational studies. It should be noted that multiple factors can still influence the strength of association observed in MR studies, such as relationships between genetic variants in CRP and CRP levels, demographic characteristics of study populations, types, and stages of CVDs.[29] However, most MR studies show that there is no association between CRP levels and CVDs.[30–32] Evidence from a meta-analysis of CRP and CVDs also supports the null relationship.[4] Therefore, we believe that no causal relationship was identified between CRP and CVDs in MR studies.

Forth, clinical trials with different anti-inflammatory treatments shed some light on the role of CRP and its relation with CVDs. Such trials were motivated by previous observational studies of the long-term administration of statins and aspirin and tested the hypothesis that inflammation can cause CVDs.[33,34] To our knowledge, four renowned clinical trials explored the effect of several anti-inflammatory treatments on CVDs and CRP, including JUPITER study,[35] CANTOS study,[36] CIRT study,[37] and COLCOT study.[38] The first three fully analyzed CRP as a secondary outcome. Specifically, JUPITER and CANTOS showed that their treatments reduce both the risk of CVDs and CRP levels. In contrast, CIRT showed no treatment effects on either CRP levels or the risk of CVDs. However, these clinical trials used a wide range of anti-inflammatory treatments that are not specific to lower CRP levels. Therefore, it is also hard to conclude whether anti-inflammatory treatments reduce the risk of CVDs by lowering CRP levels.

Inconsistent findings across studies of different designs

Based on the above examination, we found some similarities and inconsistencies in findings across studies of four designs. We found that most of the traditional observational studies and clinical trials showed a positive association between CRP and CVDs. In contrast, animal experiments showed mixed results on the association between CRP and CVDs, and most MR studies showed no positive association. These seemingly contradictory findings raised key questions in which types of studies we should believe and how their different findings can be explained. Therefore, we used Directed Acyclic Graphs (DAGs) as a conceptual representation to show how the relationship between CRP and CVDs was examined in studies of each design (Figure 1A to D).[39] These DAGs may have oversimplified designs of these studies but provide a clear and straightforward summary of them.

A close examination of these DAGs suggests that studies of each design have focused on slightly different aspects of the relationship between CRP and CVDs. First, animal experiments used genetic techniques as an instrument to examine the causal relationship between CRP and CVDs (Figure 1A). Besides mixed findings of animal experiments, another challenge is whether their findings can be generalized to human populations. Second, many traditional observational studies consistently observed a positive association between CRP and CVDs in human populations, which however did not give a good answer to whether there is a causal relationship between them (Figure 1B). This is because confounding, whether measured or unmeasured, is a major issue in these studies. Third, in MR studies, researchers used CRP gene variants as an instrument to assess a causal relationship between CRP and CVDs (Figure 1C) and concluded that there is unlikely to be a causal relationship between both CRP and CVDs. MR studies also have multiple limitations, including low statistical power, reverse causation, population stratification, and others.[40,41] Last, clinical trials of anti-inflammatory treatments observed positive associations between CRP and CVDs but did not directly examine the causal relationship between CRP and CVDs (Figure 1D). Their observed positive associations are likely to be explained by that CRP and CVDs shared a common cause of anti-inflammatory treatments. Besides studies of four designs summarized Figure 1A to D, we noticed a growing interest in studying the relationship between healthy behaviors, CRP, and CVDs.[42,43] They had some promising findings of the potential impacts of healthy behaviors on CVD, but they

did not directly assess the causal relationship between CRP and CVDs, either. These DAGs suggest that animal experiments and MR studies are more comparable to each other from a perspective of causal relationships, while traditional observational studies and clinical trials are more alike.

We believe that studies of different designs point to the same direction: CRP is more likely to be a bystander rather than a cause for CVDs. CRP is positively associated with an increased risk of CVDs due to common causes including upstream inflammatory activities. Also, it should be noted that a lack of evidence on the causal relationship between CRP and CVDs shall not preclude the use of CRP as a predictor for CVDs. What the role of CRP in the pathology of CVD is or whether CRP can be used as a therapeutic target for CVDs needs further examination in future studies.

Future directions

We want to emphasize that inflammation and immune dynamics are complex and our understanding of them is ever in flux. A major limitation of many studies on inflammation and CVDs is that the biomarkers currently used to gauge inflammation are crude and nonspecific. They reflect the downstream consequences of inflammatory activity, but do not provide information relating to the site(s) of activation and cannot be used to discriminate functionally important activation pathways. For example, while previous studies typically interpreted CRP as an inflammatory biomarker, this is not always true because it can also be elevated in the absence of a wider inflammatory response, suggesting the complex role that it plays in a range of biological processes.[44] Therefore, one or two biomarkers cannot sufficiently represent the dynamic nature of inflammation and immune function. A systems-wide approach to assess inflammation and immune functions is needed for future studies. It is challenging but necessary to make measures of inflammation that are meaningful to the pathology of interest and which can guide specific and targeted therapies.

Conclusion

Our examination of available studies suggests that CRP is unlikely to be a cause for CVDs. The widely observed associations between CRP and CVDs are more likely to be explained by confounding in observational studies and by treatments in clinical trials. While CRP is a useful biomarker in CVD risk assessment, the use of it as an effective therapeutic target needs more evaluations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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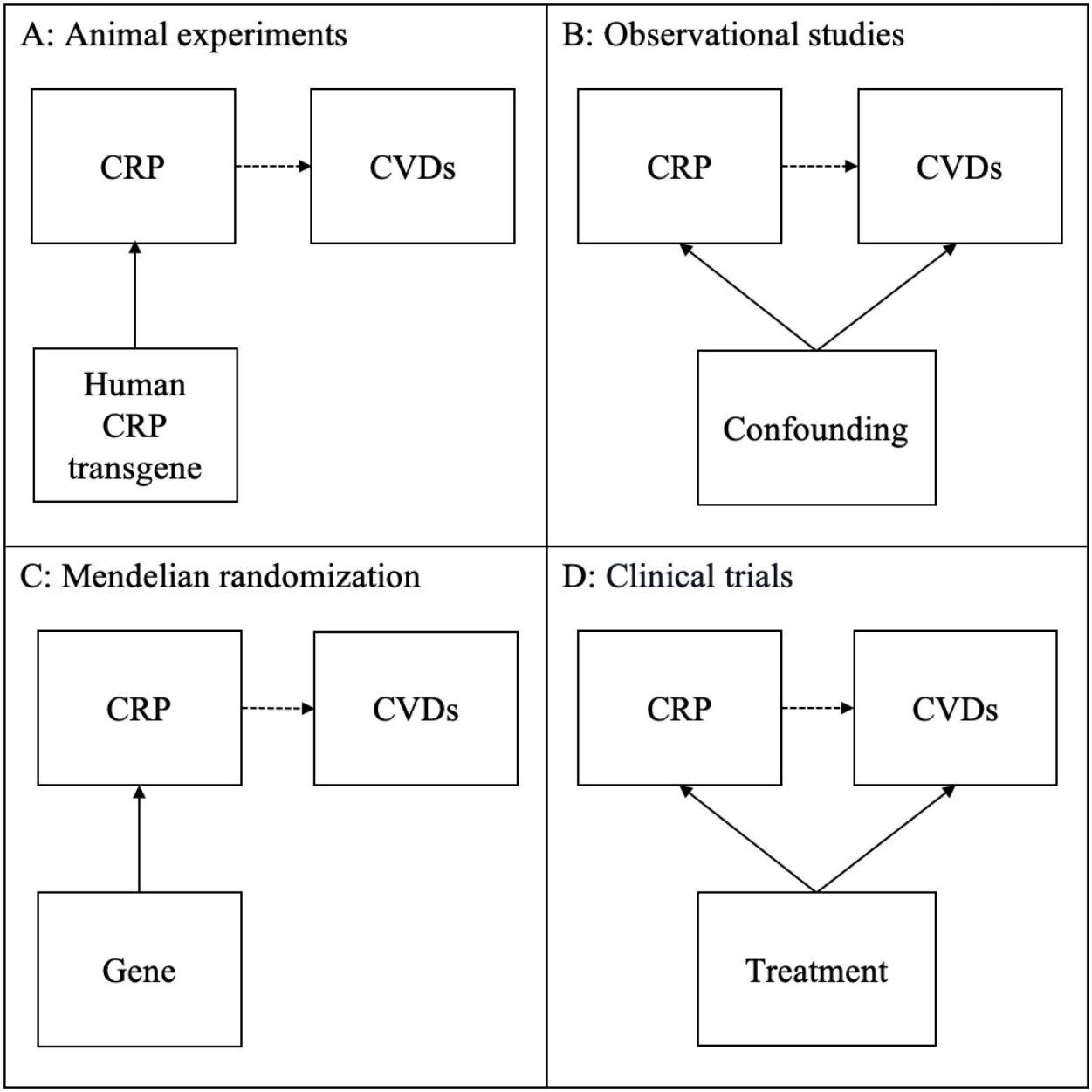

Figure 1.
The relationship between CRP and CVDs in studies by different designs

Table 1.

A summary of studies on the relationship between CRP and CVDs

Author, year	Methods to estimate associations	Subjects or study populations	Sample size (cases/all)	Main findings
Animal experiments				
Paul, 2004[17]	Compared atherosclerotic lesions between huCRPtg$^{+/}$ApoE$^{-/-}$ and huCRPtg$^{-/}$ApoE$^{-/-}$	Mice	209	CRP↑ CVD↑
Kovacs, 2007[22]	Compared atherosclerotic lesions between huCRPtg$^{+/}$LDLR$^{-/-}$ and huCRPtg$^{-/}$LDLR$^{-/-}$	Mice	105	CRP↑ CVD↓
Koike, 2009[21]	Compared the susceptibility to cholesterol-rich diet-induced aortic and coronary atherosclerosis between huCRPtg^{+} and huCRPtg^{-}	Rabbits	26	Null association
Traditional observational studies				
Rutter, 2004[24]	Compared the 7-y incidence of CVD events between highest versus lowest CRP quartile	Framingham Offspring Study in the US	189/3,037	CRP↑ CVD↑
Cushman, 2005[45]	Compared the 10-y incidence of CHD between CRP>3mg/L and CRP<1 mg/L	Cardiovascular Health Study in the US	547/3,971	CRP↑ CVD↑
Chen, 2022[46]	Compared the 4.62-y incidence of CVD among quartiles of 7-y cumulative burden of CRP	Kailuan study in China	2,118/34,959	CRP↑ CVD↑
Mendelian randomization studies				
Elliott, 2009[30]	MR between CRP and CHD	Multiple European studies	28,112/128,935	Null association
Wensley, 2011[31]	MR between CRP and CHD	Multiple European studies	46,557/194,418	Null association
Wang, 2022[47]	MR between CRP and CHD	Multiple European and East Asian studies	121,072/494,478	Null association
Clinical trials				
Ridker, 2008[35]	Compared the 1.9-y incidence of MCE between Rosuvastatin group and Placebo group	JUPITER	393/17,802	CRP↓ CVD↓
Ridker, 2017[36]	Compared the 3.7-y incidence of MCE between Canakinumab group and Placebo group	CANTOS	1,490/10,061	CRP↓ CVD↓
Ridker, 2018[37]	Compared the 2.3-y incidence of MCE between Low-dose methotrexate group and Placebo group	CIRT	408/4,786	Null association *

Footnote: huCRPtg: human CRP transgene; ApoE: apolipoprotein E; LDLR: low-density lipoprotein receptor; CHD: coronary heart disease; MCE: major cardiovascular events

* No changes in both CRP and CVD comparing treatment and control groups